REMARKS

Status of the Claims

With this amendment, claims 1-3, 8-27, 30, 31, 33, 41, 42, 45, 49, and 56-58 have been amended. Support for the amendments can be found throughout the specification and claims as originally filed, for example, at page 8, lines 32-34; and page 10, lines 4-11, 24-26, and 28-32. Claims 4-7 and 59 have been cancelled without prejudice or disclaimer. No new matter has been added.

Applicants note that the Office Action states (at page 2, last two lines) that claims 16-27, 29-40, 42-52 and 60 stand withdrawn as directed to a non-elected invention. Applicants consider this to be a typographical error, as the Restriction Requirement in the present case did not indicate that claims 16-27, 29-40, 42-52 and 60 were subject to restriction in this way (and note that claim 60 was cancelled in a preliminary amendment filed with the application).

Claims 1-3, 8-27, 30-31, 33, 41-42, 45, 49, and 56-58 are pending in the application.

Applicants note with appreciation that claims 19-27 have not been rejected over the art of record and request an indication of allowable subject matter in the next Office Action or Notice of Allowance.

Interview Summary

Applicants thank the Examiner for the courtesy of a brief telephonic interview with their undersigned representative. During the Interview, the rejection under 35 USC §112, first paragraph, was discussed. No final agreement was reached.

Rejections of claims under 35 USC §112, second paragraph

Claims 30 and 31 stand rejected under 35 USC §112, second paragraph, as allegedly being indefinite. This rejection is traversed.

Without agreeing with the rejections, claim 31 has been amended as suggested by the Examiner. Applicants further contend that claim 30 – which is directed to a compound, not a pharmaceutical composition – is clear and is not indefinite.

Reconsideration and withdrawal of the rejection is proper and the same is requested.

Rejections of claims under 35 USC §112, first paragraph

Claims 33, 41-42, 45, 49, and 56-59 stand rejected under 35 USC §112, first paragraph, as allegedly lacking enablement. Citing some of the factors set forth in *In re Wands*, the Examiner contends that undue experimentation would be required to practice the invention as claimed. This rejection is traversed.

First, Applicants contend that the Office has not adequately considered the sixth *In re Wands* factor listed at page 6 of the Office Action: the amount of direction or guidance provided.

The application as filed discloses compounds that have capsaicin modulatory activity, including many working examples, methods of making the compounds, and methods of administering the compounds to a patient for the treatment of the recited conditions. The specification further provides *in vitro* and animal model assays for confirming the compounds' capsaicin modulatory activity and assessing the analgesic efficacy of the compounds in animals. Applicants' disclosure is entitled to consideration for all that it teaches. The Office Action, however, summarily dismisses the *in vitro* and animal model experimental procedures provided in Examples 4 – 10 of the instant application[1] without explanation and does not take into account the extensive discussion of how to make and use compounds and pharmaceutical compositions of the invention, for example, the section spanning page 38, line 25 to page 50, line 4, of the application as filed. Applicants submit that the disclosure of how-to-use, together with the data and routine procedures provided in the specification, are sufficient to allow the selection of appropriate compounds and the determination of treatment protocols for the recited conditions, with only routine experimentation. Accordingly, Applicants respectfully request that the Examiner reconsider the amount of direction or guidance provided in the specification, and Applicants' enablement of the practice of the currently rejected pending method claims.

[1] The Office Action refers to pages 83-93 of the specification, but it is believed that the Office Action intended to refer to pages 74-83 or so.

Second, the Office Action does not properly consider the third *In re Wands* factor, relating to the state of the art. It is respectfully submitted that the state of the art is such that, in view of the teachings of the present specification, only routine experimentation would be required to practice the claimed invention. *In vitro* and animal models of certain conditions are described in the instant application (see, e.g., Examples 4-10). Moreover, animal models for the therapeutic indications recited in the claims were well known at the time of the present invention.

Applicants also wish to point out that efficacy in relevant animal models has, in fact, been confirmed for VR1 antagonists. The following references describe animal models for certain claimed therapeutic indications; in some cases, the references also discuss potential treatments of such conditions using VR1 antagonists.

For example, Xiang et al., (*J. Applied Physiol.*, (1998) 85:1847-54) relates to a cough response in a guinea pig. Trevisani et al. ((2004) *Thorax* 59:769-72) describes animal testing for treatment of cough, and discusses the activity of a modulator of the receptor VR1 (now known as TRPV1) in preventing cough. Similarly, VR1 antagonists are effective in animal model assays for certain airway disorders (*see, e.g.,* US 2003/0236280). Garcia-Martinez et al. ((2002) *PNAS* 99:2374-79) describes animal testing for treatment of pain, and discusses the activity of a modulator of the receptor VR1 in attentuation of pain. Honore et al. ((2005) *J. Pharmacol. Exp. Therap.* 314:410-21), also describes animal testing for treatment of pain, and discusses the activity of a modulator of the receptor VR1 in attentuation of inflammatory pain. Ghilardi ((2005) *J. Neurosci.* 25:3126-31), also describes animal testing for treatment of pain, and discusses the activity of a modulator of the receptor VR1 in attentuation of cancer pain. Nagy et al. ((2004) *European J. Pharmacol.* 500:351-369) indicates that VR1 antagonists alleviate pain (see, page 362, second column, first full paragraph) and also discusses the role of VR1 in other conditions. Sasaki et al. (*Int. J. Urol.*, (1997) 4:401-406) describes a rat model for urinary incontinence. VR1 antagonists have been shown to possess therapeutic efficacy in animal models for urinary incontinence (*see, e.g.,* WO 03/055848). PCT Patent Publication WO 04/028440 describes *in vitro* and *in vivo* testing for treatment of urological disorders, and discusses the activity of a modulator of the receptor VR1 in treatment of urinary incontinence and overactive bladder.

In addition, methods for administering compounds for the treatment of the recited conditions were well known in the art, as demonstrated, *e.g.,* by the disclosures of the Nagy reference cited above and by Szallasi et al. ((2004) *J. Med. Chem.* 47(11):2717-2723).

Copies of each of the references discussed above are enclosed herewith (except the U.S. patent application publication) and are listed on the accompanying Form PTO/SB/08.

As a further example, certain VR1 antagonists are presently being tested in human clinical trials as treatments for pain. See, e.g., http://clinicaltrials.gov/ct2/show/NCT00387140?cond=%22Toothache%22&rank=15 (accessed October 17, 2007) (clinical trial of a VR1 antagonist for post-operative dental pain).

Thus, one of ordinary skill in the art could readily use only routine experimentation to confirm the efficacy of compounds in relevant animal models and administer pharmaceutical compositions to a patient in need thereof.

Third, it should be noted that, contrary to the statement at page 7 of the Office Action that "claims 33, 41-42, 45, 49, and 56-59 [are directed to] treating a condition responsive to capsaicin receptor modulation in a patient," not all the claims are directed to methods of treating conditions in a patient. For example, claim 33 is directed to a method for reducing calcium conductance of a cellular capsaicin receptor; claim 41 is directed to a method for inhibiting binding of vanilloid ligand to a capsaicin receptor *in vitro*; and claim 42 is directed to a method for inhibiting binding of vanilloid ligand to capsaicin receptor in a patient.

In view of the scope of the claims, the amount of direction and guidance provided by the entirety of Applicants' disclosure, the sophistication of the contemporary state of the art and the high level of skill therein, Applicants believe that it is clear that only routine experimentation would be required to confirm activity of a compound in the relevant animal model, to optimize treatment parameters, and to otherwise practice the full scope of the methods of the pending claims.

Obviousness-Type Double Patenting Rejections

Claims 1-3, 8-27, 30-31, 33, 41, 42, 45, 49, and 56-59 stand provisionally rejected under the judicially-created doctrine of obviousness-type double patenting (ODP) over certain claims of U.S. Patent Publication 2007-0105865; U.S. Patent Publication 2004-0156869; U.S. Patent Publication 2005-0215575; and U.S. Patent No. 7,074,799. These rejections are traversed.

Without conceding the propriety of these rejections, Applicants will consider filing a terminal disclaimer, if necessary and appropriate, to overcome these rejections upon indication that the present application is otherwise in condition for allowance. Alternatively, Applicants reserve the right to further traverse the rejections, or to request withdrawal of the rejection(s) to permit the present application to proceed to issue if the application is otherwise in condition for allowance. In any event, Applicants note that at least some of the double patenting rejections appear to be improper or erroneous.

For example, although the Office Action states (at page 10) that the compounds, compositions, and methods of the claims of U.S. Patent Publication 2005-215575 are "fully embraced by" (emphasis in original) and "overlaps mostly significantly" with the present claims, this is not the proper inquiry. To maintain a rejection for obviousness-type double patenting, the Office must establish that the present claims would have been obvious over the claims of the reference patent or patent application. See MPEP 804. The inquiry does not involve the claims of a patent application publication; the focus is on whether the claims of the underlying patent application render obvious the claims of the present application. Thus, the proper inquiry is whether the pending claims of U.S. patent application no. 10/892,741 (the patent application which published as U.S. Patent Publication 2005-215575) render obvious the claims of the present application. Applicants contend that they do not.

The instant pending claims are directed to compounds (including salts and hydrates, and compositions and methods of use thereof) in which the compound includes at least one carboxylic acid, phosphate or phosphonate group. In contrast, the currently pending claims of the '741 application (which presently stands allowed) are directed to specific compounds (and salts thereof); none of the compounds recited in

the pending claims of the '741 application includes at least one carboxylic acid, phosphate or phosphonate group, as required by the claims of the instant application. The claims of the '741 application contain absolutely no teaching or suggestion of this feature of the presently-pending claims. The claims of the '741 application therefore cannot, and do not, render obvious the claims of the instant application, and the double patenting rejection must be withdrawn.

Further, Applicants note that in the Office Action, certain claims stand provisionally rejected under the judicially-created doctrine of obviousness-type double patenting over certain claims U.S. Patent No. 7,074,799. However, a provisional rejection does not apply when the reference claims are claims of an issued patent. Clarification is requested.

Rejections of claims under 35 USC §102(b), first paragraph

Claims 1-3 and 8-18 stand rejected as anticipated by Sobolov-Jaynes et al, U.S. Patent 6,225,318. This rejection is traversed.

Although the Office Action alleges that a particular compound shown in the Sobolov-Jaynes patent anticipates the pending claims, Applicants cannot agree. As mentioned previously, the compounds of the pending claims include at least one carboxylic acid, phosphate or phosphonate group. The cited compound of Sobolov-Jaynes does not disclose this feature of the pending claims. Applicants respectfully contend that Sobolov-Jaynes does not, and cannot, anticipate the pending claims.

Claims 1-3 and 8-18 stand rejected as anticipated by Tobe et al, WO 01/25218. This rejection is traversed.

Although the Office Action alleges that a particular compound from the Tobe application anticipates the pending claims, Applicants cannot agree. As mentioned previously, the compounds of the pending claims include at least one carboxylic acid, phosphate or phosphonate group. The cited compound of Tobe does not disclose this feature of the pending claims. Applicants respectfully contend that Tobe does not, and cannot, anticipate the pending claims.

Claims 1-3 and 8-18 stand rejected as anticipated by Carter et al, GB 2345486. This rejection is traversed.

Although the Office Action alleges that a particular compound from the Carter document anticipates the pending claims, Applicants cannot agree. As mentioned previously, the compounds of the pending claims include at least one carboxylic acid, phosphate or phosphonate group. The cited compound of Carter does not disclose this feature of the pending claims. Applicants respectfully contend that Carter does not, and cannot, anticipate the pending claims.

Claims 1-3 and 8-18 stand rejected as anticipated by Carter et al, WO 99/35146. This rejection is traversed.

Although the Office Action alleges that a particular compound from the Carter application anticipates the pending claims, Applicants cannot agree. As mentioned previously, the compounds of the pending claims include at least one carboxylic acid, phosphate or phosphonate group. The cited compound of Carter does not disclose this feature of the pending claims. Applicants respectfully contend that Carter does not, and cannot, anticipate the pending claims.

Claims 1-3 and 8-18 stand rejected as anticipated by Palanki et al, WO 99/01441. This rejection is traversed.

Although the Office Action alleges that a particular compound from the Palanki document anticipates the pending claims, Applicants cannot agree. As mentioned previously, the compounds of the pending claims include at least one carboxylic acid, phosphate or phosphonate group. The cited compound of Palanki does not disclose this feature of the pending claims. Applicants respectfully contend that Palanki does not, and cannot, anticipate the pending claims.

Claims 1-3 and 8-18 stand rejected as anticipated by Cockerill et al, WO 98/02434. This rejection is traversed.

Although the Office Action alleges that certain compounds from the Cockerill application anticipate the pending claims, Applicants cannot agree. As mentioned previously, the compounds of the pending claims include at least one carboxylic acid, phosphate or phosphonate group. The cited compounds of Cockerill do not disclose this feature of the pending claims. Applicants respectfully contend that Cockerill does not, and cannot, anticipate the pending claims.

Claims 1-3 and 8-18 stand rejected as anticipated by Barker et al, WO 97/30044. This rejection is traversed.

Although the Office Action alleges that certain compounds from the Barker application anticipate the pending claims, Applicants cannot agree. As mentioned previously, the compounds of the pending claims include at least one carboxylic acid, phosphate or phosphonate group. The cited compounds of Barker do not disclose this feature of the pending claims. Applicants respectfully contend that Barker does not, and cannot, anticipate the pending claims.

Claims 1-3 and 8-18 stand rejected as anticipated by Barker et al, U.S. Patent No. 5,580,870. This rejection is traversed.

Although the Office Action alleges that a particular compound from the Barker patent anticipates the pending claims, Applicants cannot agree. As mentioned previously, the compounds of the pending claims include at least one carboxylic acid, phosphate or phosphonate group. The cited compound of Barker does not disclose this feature of the pending claims. Applicants respectfully contend that Barker does not, and cannot, anticipate the pending claims.

Claims 1-3 and 8-18 stand rejected as anticipated by Barker et al, U.S. Patent No. 5,616,582. This rejection is traversed.

Although the Office Action alleges that certain compounds from the Barker '582 patent anticipate the pending claims, Applicants cannot agree. As mentioned previously, the compounds of the pending claims include at least one carboxylic acid, phosphate or phosphonate group. The cited compounds of Barker '582 do not disclose this feature of the pending claims. Applicants respectfully contend that the Barker '582 patent does not, and cannot, anticipate the pending claims.

Claims 1-3 and 8-18 stand rejected as anticipated by Nomoto et al, U.S. Patent No. 5,063,227. This rejection is traversed.

Although the Office Action alleges that certain compounds from the Nomoto patent anticipate the pending claims, Applicants cannot agree. As mentioned previously, the compounds of the pending claims include at least one carboxylic acid, phosphate or phosphonate group. The cited compounds of Nomoto do not disclose this feature of the pending claims. Applicants respectfully contend that the Nomoto patent does not, and cannot, anticipate the pending claims.

In addition to the foregoing, Applicants contend that the cited references (whether considered alone or in any combination) do not render obvious the claimed compounds, compositions, or methods of use.

Conclusion

Early and favorable consideration of the application is earnestly solicited.

Applicants conditionally petition for an extension of time in the event that an extension is required. The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 04-1105, under Order No. 60425 (72021).

Dated: October 18, 2007

Respectfully submitted,

By _____

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